



DATSD(CBD)

Biological Weapons and Bioterrorism Threats: *The role of vaccines in protecting the military and civilian sectors*

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Outline

- **Threats**
- **DoD Medical Biological Defense Capabilities**
- **Responses**
 - Military
 - Civilian

Potential BW Threats

Bacteria

Anthrax

Plague

Tularemia

Brucellosis

Q-Fever

Glanders

Cholera

Typhus

Shigellosis

Virus

Smallpox

Encephalomyelitis

Ebola

Marburg

Toxin

Botulinum

(Types A-F)

Staphylococcal
Enterotoxins (SEB)

Ricin

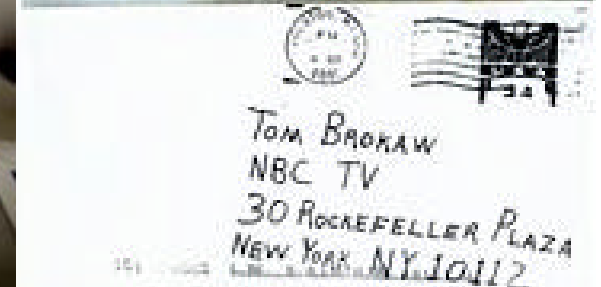
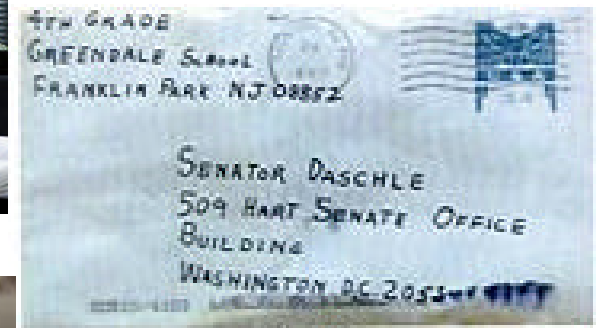
Marine
Neurotoxins

Mycotoxins

Clostridium
Perfringens

Bioterrorism Threats

...to reality.



Why Vaccinate?

- **Biological warfare (BW) agents pose high risk to military forces and operations**
 - At least 10 countries pursuing BW programs
- **Vaccines are lowest risk, most effective protection**
 - More effective with fewer adverse effects than antibiotics or other treatments
 - Enable force projection by providing continuous, long-lasting protection
- **No real-time detection systems currently available**
 - Identification delayed 15-45 minutes after exposure
- **Masks must be worn to be effective**

Requirement

- **DoD policy stated in DoD Directive 6205.3 to “...develop a capability to acquire and stockpile adequate quantities of vaccines to protect the programmed force against all validated biological warfare threats.”**

Chronology of Considerations for BD Vaccine Production

1991/92

June 93

Aug 94

Jan 95

1996

↑ (Joint Program Office for Biological Defense Established)

GOCO



- *Why Started?* Lessons From ODSS
 - No Surge Capacity for BD Vaccines
 - Limited Industry Interest
- *Why Stopped?* DOD and Congressional Directives
 - Need for Dedicated DOD Facility?
 - Most Economical Approach?

COCO



- *Why Modified?* Affordability
 - ADM Directed Cost/Benefit Analysis
 - \$450M Unfunded Requirement FY96-01
 - Industry Survey

Prime Systems Contract Approach

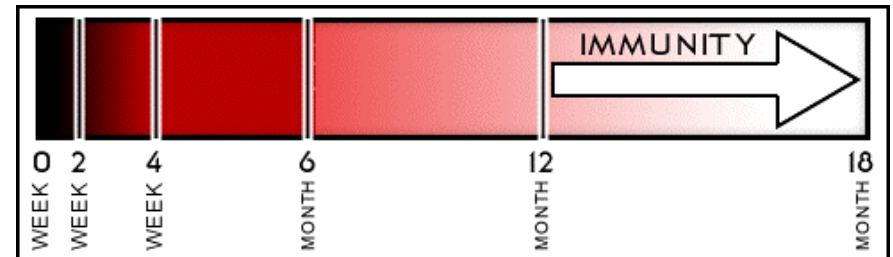
- *Why Started?* **Optimum Resource Utilization**
 - Reduces Requirement for New Facilitization
 - Enhances Competition
- Directed Prime Systems Contract Approach
- Prime System Contract Awarded (Nov-1997)

What Does Producing a Vaccine Mean?

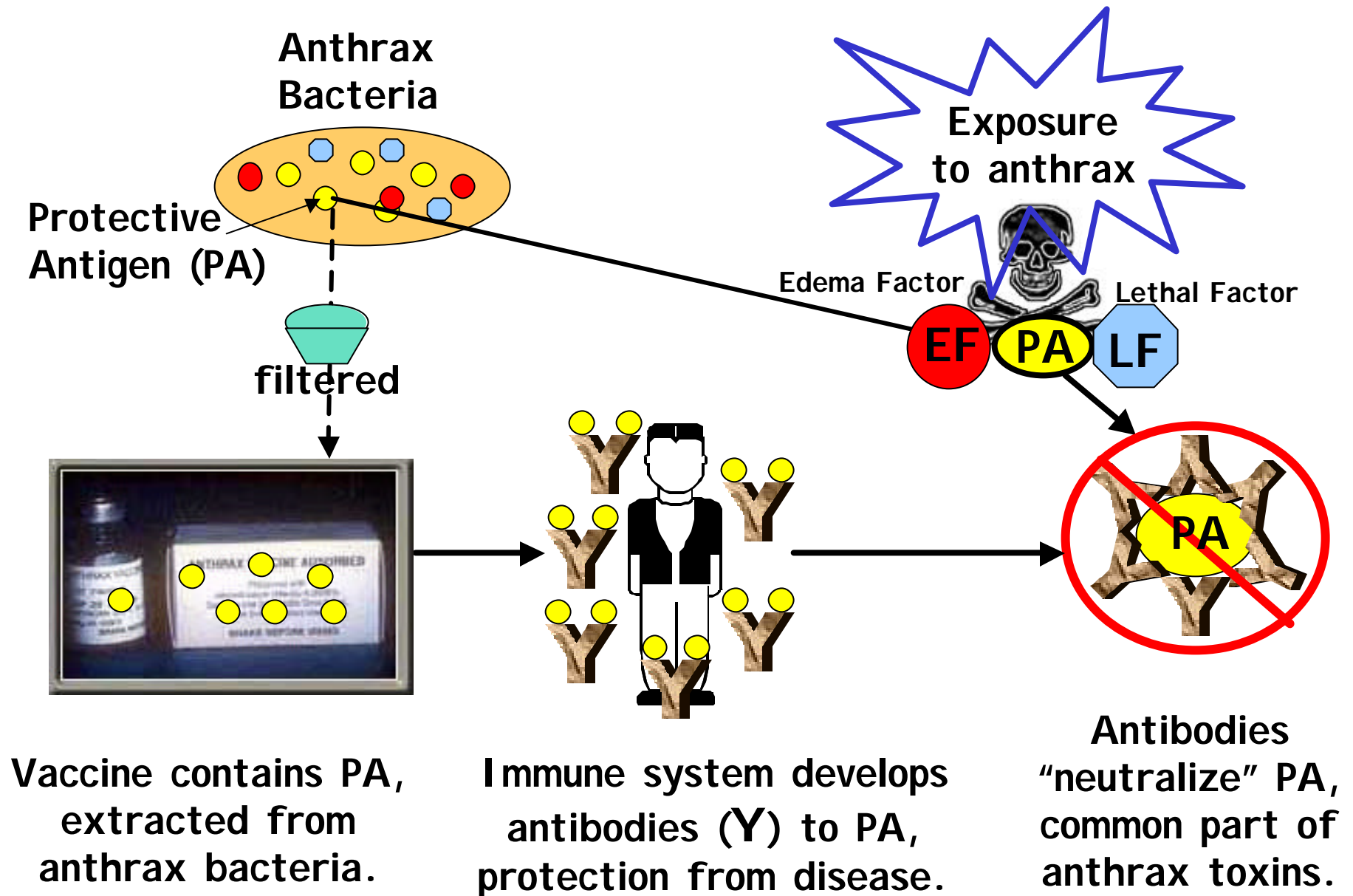
	SCIENCE & TECHNOLOGY	DEVELOPMENT & LICENSURE	LICENSED PRODUCTION
Production Approach	Bench top – many approaches	Scale up – best approach	Full Scale – fixed method
Vaccine Recipients	Lab animals (10^2-10^3)	Volunteers (10^3)	Population (10^6)
Data Management	Lab notebook	Master File: mfrng and release data, clinical trials, validation studies	Mfrng and release data, post market surveillance, adverse reactions
Stakeholders	Scientist, science manager, User	Scientist, product mgr., FDA, manufacturer, User	Warfighter, medic, logistician, FDA, mfr., product mgr.
Production Risk	Moderate	High	Low
Overall Risk	Low	High	Low–High

Anthrax Vaccine Adsorbed

- Approved by the FDA in 1970 (Only licensed BD vaccine)
- Cell-free filtrate, produced by a strain of anthrax that does not cause disease.
- Safely and routinely administered to at-risk wool mill workers, veterinarians, laboratory workers, and livestock handlers in the United States
- Manufactured by BioPort Corporation
- Currently requires 6 shots & annual booster to maintain full immunity
 - Study underway by CDC to investigate fewer doses in series (reduce to 3-4 shots)



How Anthrax Vaccine Prevents Disease



Anthrax Vaccine Efficacy against Inhalation Challenge

- Efficacy of current vaccine based on bacterial construct (that is, Protective Antigen binding to Lethal Factor and Edema Factor) not on route of exposure.
- Brachman study suggests efficacy in humans against inhalational anthrax
 - 5 cases of inhalational anthrax (4 fatal) among non-vaccinated individuals (n = 754)
 - Zero cases of inhalation anthrax among vaccinated individuals (n = 379)

Vaccine Efficacy Against Aerosol Challenge

	Vaccinated		Control	
	Number	Percentage	Number	Percentage
Rabbits	62 of 65	95	0 of 18	0
Rhesus Macaques	114 of 117	97	0 of 28	0

Concerns for Developing & Producing Biological Defense Vaccines

- **Limited interest from industry**
 - Most Public Health needs are fulfilled by the private sector
 - BD Vaccines similar to orphan drugs (interest from a few small to mid-size companies)
- **Identifying surrogate markers of efficacy**
 - Animal models used to validate efficacy of vaccines
 - Limited human efficacy data available
 - FDA review of 21 CFR requirement for Phase 3 efficacy testing in humans
 - May allow efficacy based on animal data (at least two species)
- **Large/complicated clinical studies to demonstrate safety, immunogenicity, and efficacy**

Commercial Sector Concerns

- **Unusually hazardous risks, liability and indemnification issues**
- **Small volume of business and low annual production requirements**
- **Limited commercial opportunities for BD vaccines**
- **Stringent Bio-containment requirements**
- **Biological Warfare Convention inspection requirements**
- **Government contracting and regulatory oversight requirements**

Key Features of a National Vaccine Production Facility

- **Government control of production, availability, and distribution**
- **Meets high national security priority for additional BD vaccine production**
- **Establishes a second source for anthrax vaccine adsorbed (AVA) production**
- **Overcomes limited industry interest in BD vaccine production**
- **Gov't biosafety containment facilities provide supporting R&D**
- **Flexibility for emerging production technologies**
- **Operating contractor provides specialized expertise in vaccine production and regulatory requirements**

Challenges

- **Defining production capacity requirements**
- **Defining battlefield exposure levels for Biological Warfare (BW) agents**
- **Addressing emerging/changing requirements**
 - FDA regulations
 - DoD policy
- **Cooperative development with potential international and domestic partners**
 - Aligning requirements
 - Negotiating agreements
 - Avoiding schedule impacts

Assessing Risk

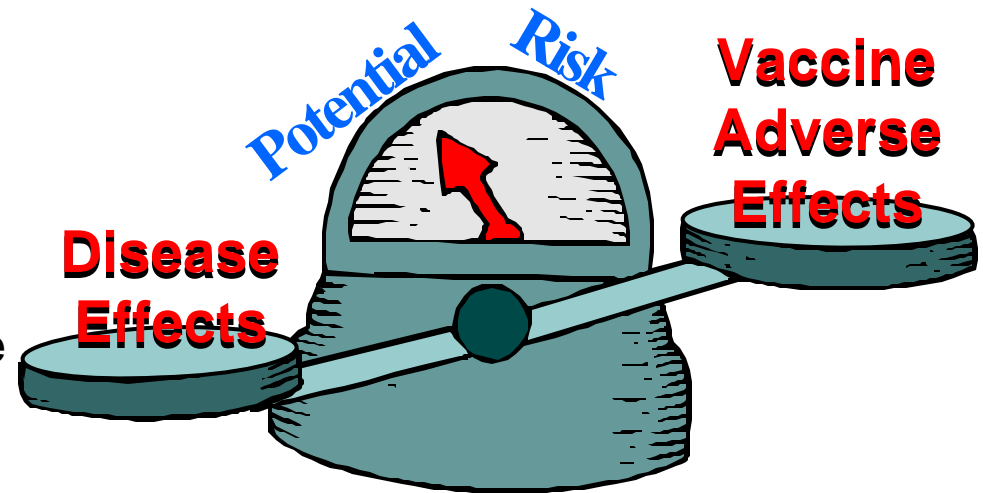
- Number of attacks against the U.S. military personnel with anthrax (or any biological weapon): **0**
- Probability (P) of attacks in the future against the U.S. military personnel with anthrax (or any biological weapon): **$0 \leq P \leq 1$**

Vaccine Use Risk Management Decisions

Naturally-Occurring Infectious Diseases

(Selected Prophylaxes)

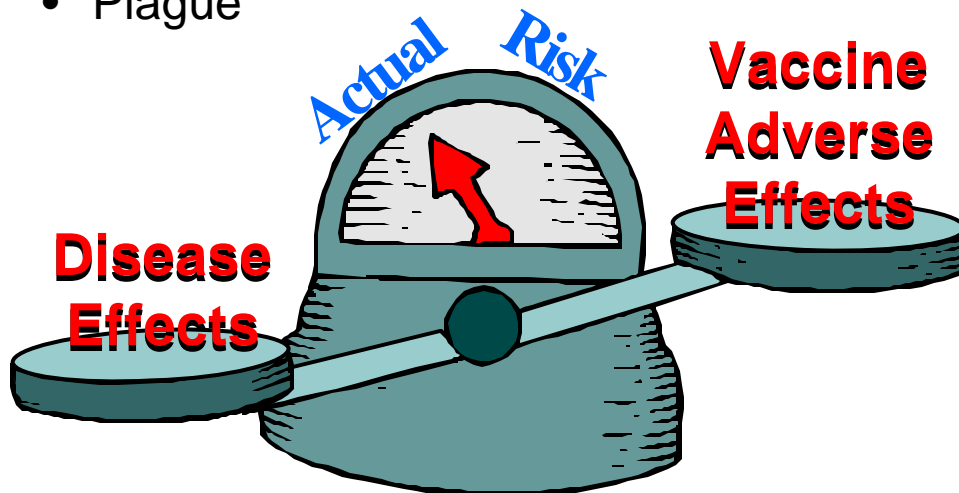
- Typhoid
- Yellow fever
- Malaria
- Diphtheria
- Tetanus
- Poliovirus
- Plague
- Hepatitis A virus
- Meningococcal disease
- Influenza vaccine
- Measles
- Mumps
- Rubella



Biological Defense Vaccines

- Anthrax Vaccine Adsorbed
- Botulinum Toxoids*
- Tularemia Vaccine*
- Smallpox vaccine (Vaccinia Virus, Cell Culture-derived)*
- Equine Encephalitis Virus Vaccines*

*Investigational New Drug (IND) status



A Complete and Comprehensive List of Risk-Free Military Operations and Activities

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-
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Limitations on Military Material Support for Civilians

- **Material designed to meet warfighter requirements may not be suitable for civilian use.**
 - Medical products must be fully licensed by the Food and Drug Administration and / or used with individual informed consent.
 - Military medical CB defense products assume a healthy adult population.
 - Some CB defense vaccines, pretreatments, and treatments may confound other medical treatments.
 - Classic “benefit-to-risk” decisions are not likely to support pre-exposure immunization of large populations against biological agents.
 - Voluntary compliance cannot be guaranteed for a large population.

Concerns for Using Biological Defense Vaccines

- **Vaccine use: Routine use vs. stockpile**
 - Limited shelf life for stockpile
 - FDA issues for maintaining license if site not involved in ongoing production
- **Undetermined health effects of administering multiple vaccines**
 - No adequate basis to assess safety, yet no basis for extraordinary concern
 - *Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces* (1996)
Institute of Medicine
- **Undetermined long-term health & safety effects**
- **Policy/Risk decision on vaccine types**
 - Live vaccines may be more effective, yet may have greater adverse effects (e.g., Oral vs. injectable polio vaccines)
- **No policy for immunizing civilian population**
 - Considerations include larger populations, pediatrics, geriatrics, immune-suppressed individuals

Parting Thoughts

- **Availability of vaccine based on several factors:**
 - Sustained resources to transition products from tech base and advanced development
 - FDA licensure of vaccine and production facility
 - Commercial interest likely to be limited – Biological Defense (BD) vaccines similar to orphan drugs
- **Implementation of vaccination**
 - Vaccination decisions will continue to have greater physiological consequences than non-medical (*e.g.*, mask on) decisions
 - Risk communication as important (if not more) than risk assessment